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THE NUMERICAL RELATIONSHIP OF *TREPONEMA PALLIDUM* TO CERTAIN PATHOLOGICAL TYPES OF CONGENITAL SYPHILIS.*†

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  - 2. Still-born.
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  - 2. Still-born.

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SUMMARY.

INTRODUCTORY.

IN a previous paper[1] I have reviewed the facts favoring the etiological relationship of *Treponema pallidum* to syphilis. Further work has offered nothing which would lead to a change in the conclusion reached at that time, namely, that *Treponema pallidum* must be considered the cause of lues. The classification of neonatal syphilis attempted in this paper is dependent entirely upon the establishment of the causal relationship of the organism to the disease, since the determination of the luetic nature of certain of the cases is not possible without the demonstration of the organism.

RESULTS OF THE ROUTINE EXAMINATION OF ALL FETAL AND INFANTILE MATERIAL FOR TREPONEMA PALLIDUM.

In working with material from fetuses and infants supposedly syphilitic I was early struck by the comparatively large number of

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[1] *Jour. Cutaneous Dis.*, 1907, 25, p. 429.

cases in which the clinical diagnosis was hereditary lues, in which there were certain pathological changes that might be considered syphilitic, but which failed to show *Treponema pallidum.* It seemed necessary, therefore, in order to arrive at a proper diagnosis, to use the Giemsa and the Levaditi methods as routine procedures on all fetal and infantile material which came to my hands. Such a routine technic soon brought out a second striking fact, namely, the presence of *Treponema pallidum* in cases which show none of the pathological changes that permit one to make a histological diagnosis of syphilis.

Working in this way I was led to make the statement, in the paper referred to above, that the clinical diagnosis of hereditary syphilis is wrong in a rather large proportion of cases. Further work forces me to reaffirm this belief, but in so doing I have no wish to wound the feelings of the clinician. For the proper recognition of any condition the clinician is dependent, ultimately, upon the pathologist. If the latter errs, the clinician must necessarily follow along the mistaken path blazed out for him. Too often the clinical diagnosis of congenital lues is based upon a suspicious parental history, desquamation of the superficial epidermis of the palms and soles, congestion and eruption of the skin of the buttocks, a palpable spleen, inflammation about the finger nails, rhinitis, and possibly ulceration of the buccal mucosa. That such manifestations can and do often occur cannot be doubted, but that any or all of them are evidences only of syphilis and that they are not met with in non-specific conditions must be doubted. In by far the greater part of my material I have had to deal with illegitimate children, and one is apt to take a syphilitic history on the part of the parents for granted in such cases. When a woman gives birth to an illegitimate child it is quite evident that she must "admit exposure," even if she does "deny lues." While women who practice more or less promiscuous prostitution certainly do run very strong chances of infection, the latter does not necessarily occur in every case, and a diagnosis which rests upon the mere possibility of contagion is apt to be based upon insufficient grounds.

In the liability to be misled by the parental history and the clinical manifestations the clinician and the pathologist react upon each other. The latter, having a clinical diagnosis of lues before him, confirms it if he finds chronic fibrosis of the spleen, chronic interstitial changes in the lungs, enlargement of the liver, or more or less well-marked irregularity of the ossification lines. The clinician, having been confirmed in his diagnosis, is not to be blamed if he considers all other similar cases syphilis. As long as the histological diagnosis is based upon the presence of changes of a chronic inflammatory nature, mistakes will be made in two directions Firstly, there are undoubtedly cases which do not show such changes but which certainly are syphilis, and secondly, there are cases which do show such chronic inflammatory lesions but which certainly are not syphilis. Now that the etiological agent concerned in the disease is known, the making of a diagnosis can be approached with greater scientific precision than has heretofore been possible, and I feel sure that the histopathology of syphilis will undergo even greater revision than has that of tuberculosis.

When there is present the classical pathological complex: pneumonia alba, fibrosis of the spleen, chronic interstitial hepatitis, proliferation of the interstitial tissue of the kidneys, osteo-chondritis, and skin lesions often of a bullous or pemphigoid character, there is little chance for error in the pathological diagnosis. But when only one or several of these changes are found the matter becomes more difficult.

CHRONIC INFLAMMATORY CHANGES WHICH MAY LEAD TO ERRORS IN DIAGNOSIS.

A chronic interstitial pneumonia, strikingly like the pneumonia alba of Virchow, is extremely common in children dying within the first two or three months after birth. There is the same fibroblastic proliferation of the septa, leading to swelling and desquamation of the alveolar epithelium and to final complete obliteration of the air spaces, and there may be just as marked a degree of lymphoid infiltration. That the only essential and characteristic change in syphilis is the vascular involvement will be discussed later. When the connective tissue proliferation in the lung becomes marked, the vascular changes form a very small part of the microscopic picture, and may, indeed, become impossible of recognition in an advanced pneumonia of undoubted syphilitic origin. It is true that in the non-specific interstitial pneumonias referred to here the pathological change begins in the posterior portions of the lungs and may remain limited to them. It is not unusual, however, to find practically all of the lower lobe and a considerable portion of the rest of the lung involved. The syphilitic pneumonia likewise begins in the lowermost regions of the lungs, and need not involve a very great amount of lung tissue. The non-specific change under discussion occurs in infants who do not thrive and in whom there is well-marked hypostatic congestion. Whether the pathological change is produced in a purely mechanical manner by the chronic congestion alone, or whether it may possibly be due in some cases to bacterial infection I am not in position to decide at the present time. That the condition is a chronic inflammatory process is certain. The mechanical factor, the hypostatic congestion, also acts in the syphilitic pneumonias, and I see no reason why it may not account for a great part of the interstitial change which occurs in pneumonia alba. Unless vascular involvement takes a fairly prominent part in the picture it becomes impossible to decide, upon purely histological grounds, as to the specific or non-specific character of the pneumonia.

The determination of the syphilitic nature of a fibrous lienitis in any given case may also be a matter of considerable difficulty. Moderate enlargement of the spleen, due to an increase in the amount of the stroma and to endothelial proliferation, may happen independently of syphilis. In some cases the proliferative change is at the expense of the lymphoid tissue and may lead to almost complete disappearance of the Malpighian bodies. In other cases the latter also are hypertrophied—all the elements of the spleen seem to be equally involved. Of course, if characteristic arteritis and phlebitis are marked, the proper diagnosis is easily made. But even in cases in which *Treponema pallidum* is present in the spleen the vascular involvement may be masked or hidden by the diffuse stroma proliferation.

As to the difficulty in making a histological diagnosis of syphilitic osteo-chondritis so experienced an investigator into the pathology of bone as Schmorl has given testimony. When considered in connection with changes in the other tissues and organs one, as a rule, does not hesitate to affirm the specific nature of bone lesions in congenital lues. And yet, when the bone lesion is studied by itself, it is extremely difficult to say just what change is characteristic of syphilis. I have several times seen, more particularly in fetuses born dead near the end of pregnancy, in cases in which *Treponema pallidum* could not be demonstrated, changes in the long bones which manifested themselves by an opacity and thickening of Guerin's line recognizable by the naked eye. Microscopically, there is irregularity of and variation in the thickness of the zone of preliminary calcification, irregularity of the zone of advancing ossification, and an increase in the number of lymphocytes of the marrow. The proper interpretation of changes of this nature is a matter of difficulty. If one believes, with Schmorl, that rachitis is a disease of post-fetal life, the change is not due to rickets, because all the cases in which I have observed it have been still-born fetuses or infants dying within a short time after birth. Moreover, I have not been able to detect the overproduction of uncalcified osteoid tissue, a change which, according to Schmorl, must be present in order to permit one to make a diagnosis of rickets. A priori, I can see no reason why the imperfect and irregular ossification that characterizes this disease might not begin during fetal life. "Fetal rickets" has been described, but the majority of competent observers deny that it has anything to do with the rachitis of post-fetal life. Under the designation, "fetal rickets," are included cases of chondrodystrophia fetalis and of osteogenesis imperfecta. Both conditions are associated with skeletal deformities. These were not present in my cases. As stated above, the changes noted consist of variation in the thickness of the zone of preliminary calcification, irregularity of the zone of advancing ossification, and an increase in the number of marrow lymphocytes, without any noticeable overproduction of osteoid tissue. The lesion seems to be either a very early chondrodystrophia fetalis or, possibly, a true rachitis beginning during intra-uterine life.

In discussing the chronic interstitial pneumonias the statement was made that in a true syphilitic pneumonia alba it is practically impossible to say how much of the change is due to syphilis and how much to the factors which produce the non-specific type of pneumonia. A difficulty of the same kind is encountered in attempting to explain a syphilitic osteo-chondritis. That *Treponema pallidum* may be present in the area of pathological change is known. And yet, in one of my cases of fetal lues which shows numerous organisms, the lower end of the femur shows no treponemata, although there is irregularity of calcification and ossification, and an increase in the number of lymphocytes. It is possible that the bone lesion in this case is not really syphilitic, but is an example of the non-specific change just discussed.

Chronic interstitial inflammatory changes in the liver and the kidneys, not associated with syphilis, are rare. There have been no such cases in my own material.

One other condition, which may, perhaps, be termed a chronic lymphadenitis, deserves mention, since it might lead to error in the histological diagnosis of lues. I have seen two such cases, one an infant dying a few hours after birth, the other several days after birth. In both syphilis was suspected, but no treponemata could be found, either by the Giemsa method on smears or by the Levaditi impregnation method. In the mesenteric and retro-peritoneal lymph glands the stroma is markedly prominent, the sinuses and capillaries are dilated, and lymphoid cells, particularly small mononuclears, are present in very small numbers. Furthermore, the intestinal lymphoid tissue shows similar changes, and the number of lymphocytes in the bone marrow and in the spleen is smaller than normal. In speaking of these changes as chronic lymphadenitis the term is used for the sake of convenience. I am not convinced that they are inflammatory in nature. One must consider the possibility of a fetal mal-development of lymphoid tissue throughout the body. An enumeration of the lymphoid cells of the circulating blood might help one in arriving at a proper conclusion as to the nature of the condition. Unfortunately, this was not done in the two cases here considered.

In a nearly full-term still-born fetus the pancreas shows a marked increase in interstitial tissue. The latter is rich in young connective tissue nuclei and in lymphocytes, and newly formed blood vessels are fairly numerous. The spleen in this case shows some increase in the amount of stroma. *Treponema pallidum* could not be demonstrated.

I have attempted to set down changes, most of them of a chronic inflammatory nature, occurring in various organs. The changes are such as to lead to difficulty in making a histological diagnosis of congenital lues. Such experience as I have had, based upon autopsies of over one hundred fetuses and newly born infants, makes me extremely skeptical as to my own ability to state definitely that a given chronic inflammatory change in a given single organ is due to syphilis. I am unwilling to consider the lesion specific unless *Treponema pallidum* can be shown to be present by the silver nitrate method. It may be argued that, in general, one would not make a histological diagnosis of syphilis, based upon changes limited to any one organ. I am willing to admit that there is little chance for error if the lungs, liver, spleen, and bones show the changes that are considered characteristic. But if one demands this complex for the establishment of a diagnosis he will fail to recognize the luetic nature of a considerable proportion of cases. Some of these will show no change, a group to be considered in more detail later. In other cases there is pathological change, but it is limited to a single organ, and often is slight in extent.

As to the proper explanation of the causation of the non-specific changes under discussion, I am not yet ready to hazard a very definite opinion. The question is the subject of other investigations already begun. When these changes occur in infants born alive and dying within the first few weeks, the clinical history will show that one is dealing with children who have never thriven and who have not received the proper returns from their food. Their physical condition is that of marasmus. The interstitial pneumonia in such cases may find an adequate explanation in a chronic hypostatic congestion. The interstitial change in the spleen, the slight abnormalities at the ossification lines of the long bones, and the marked degree of parenchymatous degeneration which may be present in the liver and the kidneys may express, in part, the disturbed metabolism of the infant. Faulty assimilative processes may also help explain those bone lesions present in still-born fetuses in whom *Treponema pallidum* cannot be found.

It may be argued that some of these conditions, which are here grouped together as non-specific, are really syphilitic and that the organisms have disappeared from the tissues. This seems improbable. So long as necrosis is not marked, the organisms can readily be demonstrated, and their presence in a non-necrotic lesion is the only criterion of the luetic nature of the inflammation.

THE ESSENTIAL PATHOLOGICAL CHANGE IN SYPHILIS.

If the chronic interstitial inflammations discussed above cannot be considered characteristic of syphilis, is there any histological change which may be considered specific? Among the host of investigators who have studied the histopathology of acquired syphilis there is unanimity in the opinion that the primary and essential change is vascular involvement. There has, of course, been a considerable amount of controversy, but this resolves itself into discussion as to whether the change begins in the lypmhatics, the veins, or the arterioles, and, secondly, as to whether the lesion is primarily an endo-, a meso-, or a perivascular one. The study of the localization of *Treponema pallidum* in the organs and tissues of hereditary lues has added much of importance to our knowledge of the pathogenesis of the disease. The silver nitrate method shows that, in spite of the more or less widespread distribution of the organisms, the chief and characteristic localization is a perivascular one. Moreover, examination of suitable material shows that the earliest pathological lesion is likewise perivascular. The earliest change is a swelling of the endothelium of the perivascular lymph spaces. This is soon associated with beginning connective tissue proliferation and with a moderate degree of lymphoid infiltration. In this early stage eosinophilous leucocytes may be present in considerable numbers. The lesion begins with the localization of *Treponema pallidum* in the perivascular lymphatics. The organisms apparently leave the lumina of the blood vessels as rapidly as possible, and then mutiply in the lymphatics. This characteristic localization of the organisms occurs not only about the blood vessels, but also in the peribronchial lymphatics and in those about the bile ducts. *Treponema pallidum* may be so numerous in these situations that, in silver nitrate preparations, the blood vessels, bronchi, and bile ducts may be seen with magnifications as low as one hundred diameters as spaces heavily outlined in black. From the perivascular lymphatics the organisms spread in two directions. They penetrate the wall of the vessel, being less numerous in the media than in the adventitia, and still less numerous in the intima. They also migrate away from the vessel and invade the tissues about it. This spread of the organisms goes hand in hand with a spread of the inflammatory process, which manifested itself first as a moderate proliferation and infiltration in the adventitia of the vessel. The fixed cells of the media and of the intima proliferate, the endothelium undergoes first hypertrophy and then hyperplasia, and lymphocytes make their appearance. The vascular inflammation may reach a grade so extreme that the tissues of the vessel wall become widely separated and almost completely hidden by a dense infiltration of lymphocytes. So marked an infiltration of the vessel wall is, however, very infrequent. The spread of the organisms into the tissues about the vessels is associated with a chronic interstitial inflammation, manifested by connective tissue proliferation and by lymphoid infiltration. In congenital syphilis, because of the widespread localization of the organisms, the diffuse chronic inflammatory portion of the process soon predominates. The primary, essential vascular involvement becomes masked and, finally, so completely hidden as to be recognized with extreme difficulty. When this stage is reached caution is necessary in making the pathological diagnosis, because of the similar appearances produced by the non-specific inflammations discussed earlier. Personally, I would feel much more certain of the correctness of a histological diagnosis of congenital syphilis based upon very slight but characteristic vascular involvement than upon an advanced pneumonia alba.

THE NUMERICAL RELATIONSHIP OF *Treponema pallidum* TO NEONATAL SYPHILIS.

As has been stated earlier in this paper the routine examination of all fetal and infantile material for *Treponema pallidum* brought out two facts of considerable importance. Of these, the first, the occurrence of non-specific chronic inflammatory lesions, not to be distinguished histologically from those of undoubted syphilitic origin, has already been discussed. The second, the presence of organisms in cases which show none of the changes characteristic for lues, remains to be considered. Because of the presence of *Treponema pallidum* in cases which show little or no pathological change it becomes possible to group certain of the cases of hereditary lues. It is to be borne in mind, however, that reference is made only to neonatal syphilis, that form of the disease in which the infection is manifested at birth or shortly thereafter.

The cases with which I have worked fall easily into two groups. The first group includes those cases which show undoubted lesions of a chronic inflammatory nature. Because of the nature of the pathological change we can designate this group "chronic."

The second group shows none of the histological changes characteristic of lues, and I do not think that a histological diagnosis of syphilis is possible or justifiable in these cases. This group, because of the slight degree, or the entire absence of characteristic pathological change, we can designate "acute." I wish it to be clearly understood that the terms "chronic" and "acute" are used only for the sake of convenience to refer to the pathological types of the disease, and that they have no reference to the possible clinical duration of the disease.

To each group belong still-born infants, as well as those born alive. I realize that I am upon dangerous ground when it is attempted to decide that a macerated, still-born fetus does not show the chronic inflammatory evidences of lues. Certain cases, born dead and showing more or less well-marked maceration, may give evidence of chronic inflammation by connective tissue proliferation, lymphoid infiltration, and the other changes associated with neonatal syphilis. In these the proliferating stroma and the infiltrating lymphocytes stain sufficiently well to be recognizable, even when the parenchyma, particularly that of the liver, has practically entirely disappeared. The occurrence of encapsulated gummata in macerated still-born fetuses is not so extremely rare. Other cases show no inflammatory changes, but only the maceration produced by autolysis. It may be argued that the inflammatory tissue in such cases has also undergone autolysis. I have not, however, been able to convince myself that this has occurred in the so-called acute, still-born cases that I have studied. In chronic cases showing much more advanced and complete maceration than was present in any of those that I have placed in the acute group, the inflammatory tissue is still to be made out, whereas this is not true of the latter group. Mere macroscopic enlargement of the macerated liver, spleen, or other of the internal organs of a still-born fetus is not sufficient basis for a diagnosis of hereditary syphilis. Such enlargement is due to absorption of fluid. It is a part of the process of maceration, and may be just as marked in cases which are certainly not luetic as in those in which the disease is present.

In the chronic group *Treponema pallidum* bears a close relationship, as regards its localization, to the lesions. The organisms are most numerous at the advancing margins of inflammatory zones, and are least numerous in older lesions in which necrosis has begun. Their number varies, of course, with the individual case, but it is never so great as to render impossible the enumeration of organisms present within any given oil immersion field. In the acute group, on the other hand, the parasites may be exceedingly numerous. They may be distributed throughout the various organs of the body, and in any oil immersion field, selected almost at random, their number may be so great that enumeration is impossible.

In the grouping which follows, the chronic group includes only such cases which show undoubted evidences of chronic inflammation. The acute group includes cases which show absolutely no change of this kind whatever or, at most, a very slight and early involvement of the blood vessels of one or more of the organs.

A. Cases Showing Chronic Lesions.

1. *Born living.*—Of the chronic cases born alive Fig. 1 shows the small number of organisms present in any single field of a well-marked pneumonia alba.[1] The septa are greatly thickened and in the larger portion of the lung the air spaces are completely obliterated. It is of interest to compare Fig. 1 with Fig. 2, both being derived from the same case. Fig. 2 is from the wall of a branch of the portal vein within the liver. The vessel wall shows a diffuse lymphoid infiltration so intense that it is almost impossible to detect any of the original tissue elements. There is very little connective tissue proliferation. Judged by the standards of pathological histology this lesion is not of so long duration as the lung change. From Fig. 2 it will be seen that the number of organisms is considerably greater in the more recent lesion than in the older one.

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[1] It will be noticed that there is some variation in the thickness of the organisms, even in photographs made with the same magnification. This is due to differences in the readiness with which the various tissues are penetrated by the impregnating fluids. The possibility of the presence of spiral organisms other than *Treponema pallidum* has been excluded in every case by the use of the Giemsa method upon smears made from the organs at the time the autopsies were performed.

Chronic syphilitic inflammation of the spleen usually results in a considerable relative decrease in the number of lymphocytes and their replacement by the cells and fibers of the stroma. The proliferation is, as a rule, so diffuse that it is impossible to determine whether the blood vessels show characteristic involvement. Fig. 3, from such a spleen, shows only a single treponema within the field.

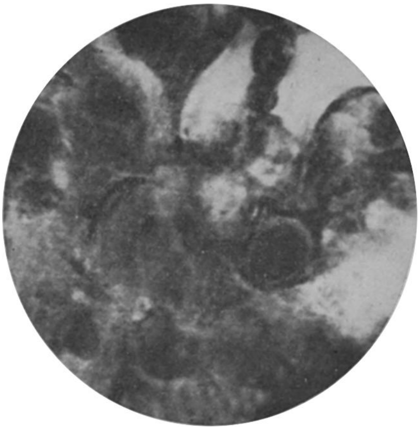

FIG. 1.—Well-marked pneumonia alba. ×1,500.

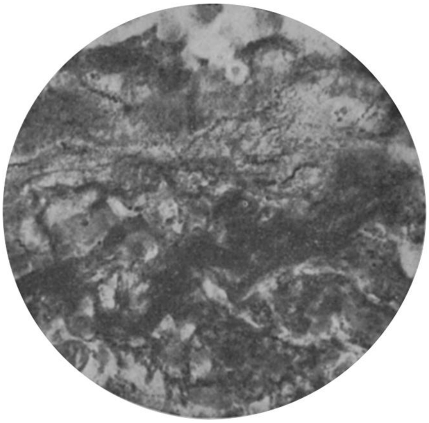

FIG. 2.—From a branch of the portal vein which shows intense lymphocytic infiltration. ×1,500.

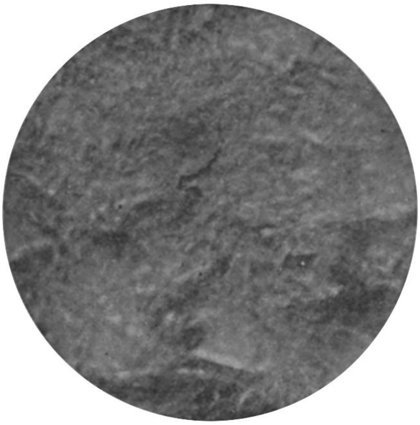

FIG. 3.—From a chronic lienitis which shows disappearance of lymphoid cells and diffuse increase of stroma. ×1,500.

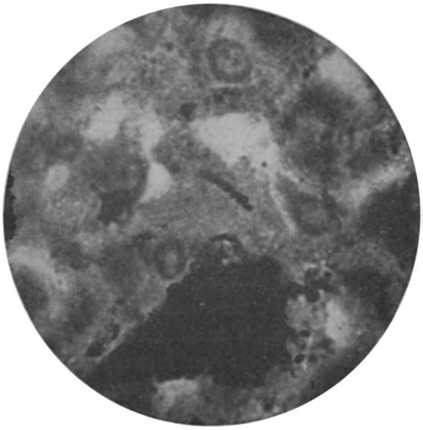

FIG. 4.—A very early miliary pericapillary gumma of the liver. ×1,500. The black mass is a necrotic liver cell.

In one case included in the chronic group, an infant which died three weeks after birth, the liver shows miliary gummata of an earlier stage than I have ever seen in acquired syphilis. The lesions bear a very definite relationship to the capillaries, either entirely surrounding a capillary or being situated at one side of it. They are composed of fibroblasts, polymorphonuclear eosinophiles, and lymphocytes intermingled with each other. Necrosis is absent or is limited to individual liver cells.

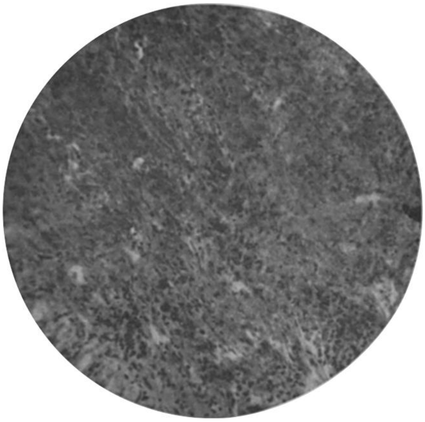

Fig. 5.—Portion of the fibrous capsule of a necrotic gumma of the lung. ×100.

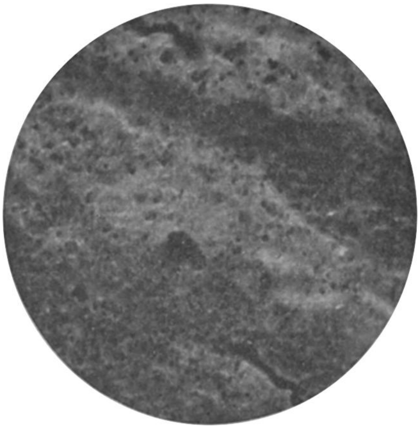

Fig. 6.—From the tissue shown in Fig. 5. ×1,500.

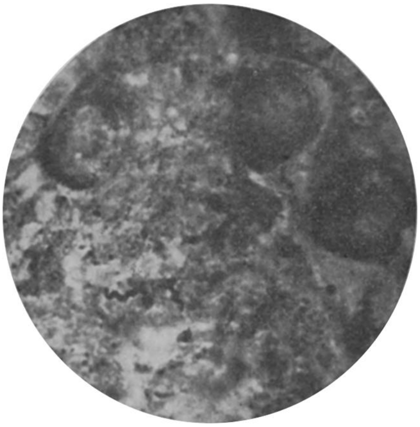

Fig. 7.—From a thickened and infiltrated alveolar septum of the lung. ×1,500.

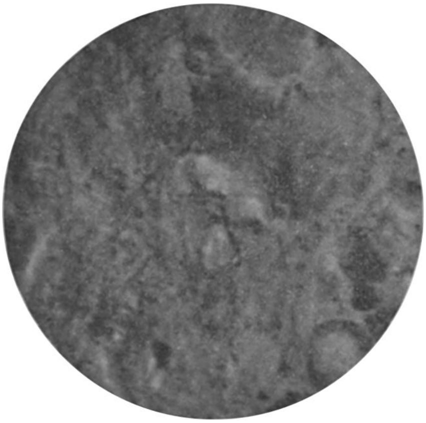

Fig. 8.—From a spleen which shows few lymphocytes and increased prominence of the stroma nuclei. ×1,500.

The centers of the gummata, even at such an early stage, show very few organisms, as appears from Fig. 4. At the periphery, within liver cells, they may be somewhat more numerous.

2. *Still-born.*—The still-born chronic group offers interesting preparations, more particularly when a comparison is made with those derived from the still-born acute

group. Fig. 5 is the thick, fibrous, infiltrated capsule of a necrotic gumma of the lung. Fig. 6, from a portion of the capsule, shows two organisms. They are thick, the spirals are irregular and in part lost. As the result of many investigations it is well known that *Treponema pallidum* decreases rapidly in numbers in the skin lesions of the late secondary stage of the acquired disease, that is, when necrosis begins. It is present in exceeding paucity in the necrotic gummata of acquired lues. This disappearance of the organisms with the beginning of necrosis may be partly due to an active migration away from the lesion. Fig. 6 indicates that the decrease is in part, possibly in large part, due to degeneration and death of the organisms themselves, caused by the same processes which induce the tissue death. Fig. 7 shows two organisms in a field from an alveolar septum of the lung. Lymphocytes are numerous and the septum is thicker than normal.

Fig. 8 is from a spleen in which maceration has proceeded to such an extent that only the nuclei of the lymphocytes and of the fibrous stroma stain. The stroma is prominent.

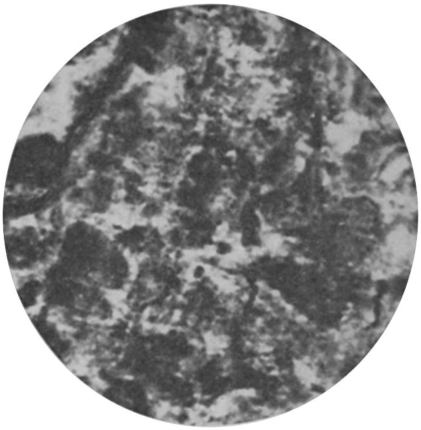

FIG. 9.—From the periglomerular connective tissue of the kidney. The interstitial tissue is greatly increased in amount and is rich in young spindle nuclei and in lymphocytes. ×1,500.

Fig. 9 illustrates the small number of organisms present in the periglomerular connective tissue of the kidney. The organs of the fetus from which the preparation was derived were so macerated that the parenchyma cells are not stainable. In the kidney the tubules are recognizable only as unstained, granular areas. The glomerular nuclei still stain well. Newly formed connective tissue infiltrated with lymphocytes widely separates the glomeruli and the tubules.

B. CASES SHOWING NO CHARACTERISTIC LESIONS.

1. *Born living.*—My material illustrating the acute, born-living group is limited to one case, an infant which died a few days after birth. For two or three weeks previous to her confinement the mother had complained of a loss of hair and of sore throat. Six weeks after the birth of the child she developed a typical skin eruption. The lungs of the infant show an acute pneumonia of lobular type, but absolutely none of the histological changes which might warrant a diagnosis of lues. Fig. 10 gives some idea of the richness of the pulmonary tissue in organisms. The spleen shows only acute congestion, but many treponemata. The adrenal, Fig. 11, is also rich in organisms. The only organ which shows any histological change that may be considered specific is the liver. Some of the vessels are surrounded by a narrow zone in which there is a very moderate grade of lymphoid infiltration. In comparing Fig. 1 with Fig. 2, both from a chronic case, the statement was made that treponemata are con-

siderably more numerous in the liver, the organ in which the lesions are, pathologically speaking, more acute than in the lung, the seat of more chronic changes. The same is true for the acute case under consideration. Whereas organisms are numerous in those organs which show no specific change, they are present in small numbers in the the liver (Fig. 12), the only organ which shows any characteristic lesion.

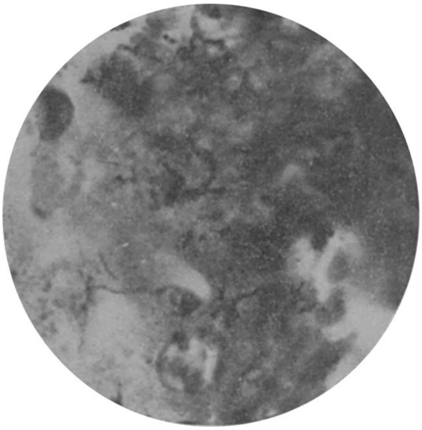

Fig. 10.—From the bronchial cartilage of a lung which shows no chronic change. × 1,800.

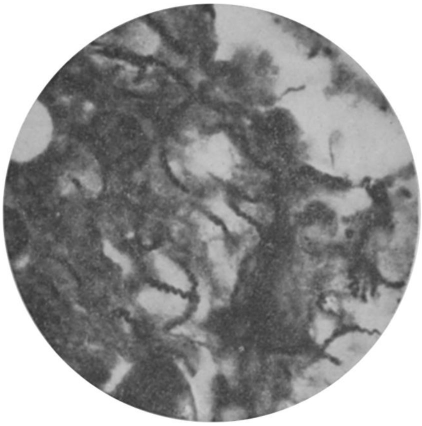

Fig. 11.—From an adrenal which shows only congestion of the medulla. × 1,800.

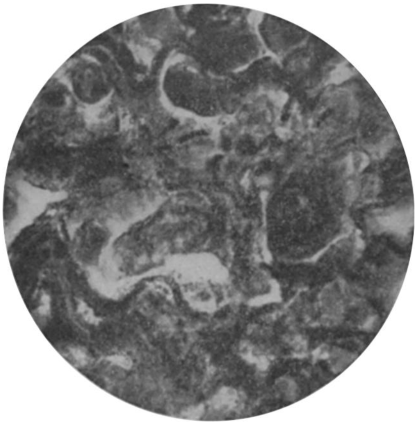

Fig. 12.—The wall of a branch of the portal vein. × 1,500.

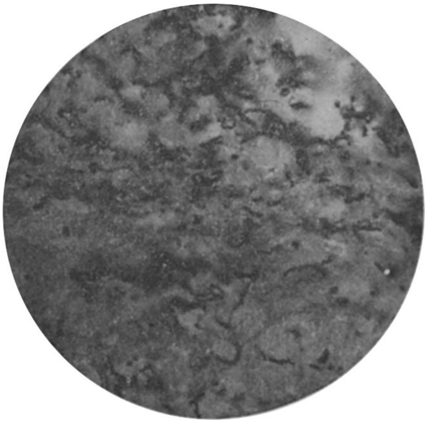

Fig. 13.—From a lung which shows maceration but no chronic change. × 1,500.

2. *Still-born.*—The remaining photographs were made from the tissues of fetuses, none of whose organs show any histological inflammatory changes. Fig. 13 is from an alveolar septum of the lung of a fetus of approximately the same age as that from which

Fig. 7 is derived. Maceration was about equally marked in the two cases. The septum illustrated in Fig. 13 is of normal thickness and shows no increase in lymphoid cells or in fibroblasts.

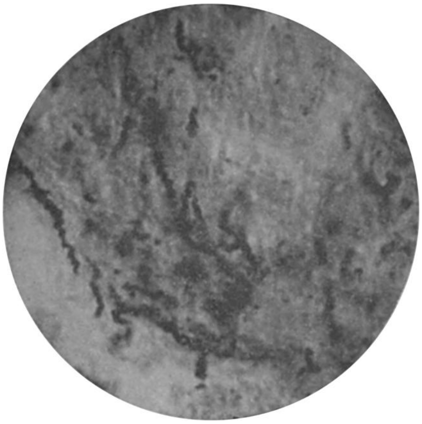

FIG. 14.—Spleen. Although maceration is present the stroma nuclei stain and are not increased in number.

Fig. 14 is to be compared with Figs. 3 and 8. In the spleen of Fig. 14 the nuclei of the small lymphoid cells and of the connective tissue cells still stain fairly well. The stroma is not unduly prominent. A comparison of Fig. 14 with Figs. 3 and 8 may help in establishing the chief point under discussion, the numerical relationship of *Treponema pallidum* to two well-characterized groups of neonatal syphilis.

Furthermore, compare Fig. 15 with Fig. 9. The kidney from which the former is derived shows no periglomerular or interstitial change, yet organisms are numerous. None of the organs of the fetus from which the kidney of Fig. 15 comes shows any greater inflammatory change than does the kidney. Treponemata are as numerous in all the other organs as they are in the kidney.

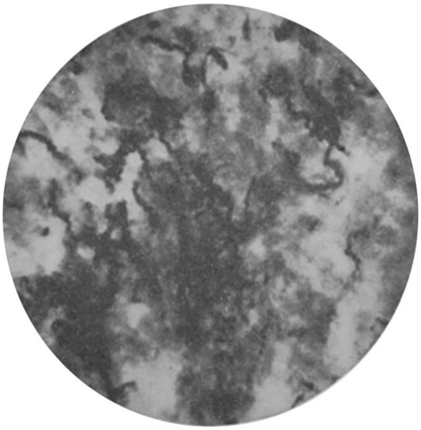

FIG. 15.—From the peri-arterial tissue of the kidney. The interstitial tissue of the organ is not increased.

In the preparation of the photomicrographs the attempt was made to select representative fields, fields which would make possible a just comparison between the cases showing chronic inflammatory changes and those showing no specific change. The preponderating number of organisms in the latter group is even more striking when the sections themselves are studied than appears from the photographs. It is well to state explicitly that I do not wish to maintain that every case of neonatal syphilis which shows well-marked chronic lesions will be characterized by a paucity of organisms. Although all of the chronic cases studied by me do show small numbers of treponemata, as compared with those cases which show no chronic lesions, there is no reason why a chronic inflammatory process might not be associated with a large number of parasites. To properly explain such a case, however, it would be necessary to suppose a moderate infection leading to tissue reaction, followed by a subsequent rapid multiplication of organisms. Such a condition is exactly comparable with a bacteriemia following a chronic abscess, an acute generalized miliary tuberculosis following a chronic ulcerative tuberculosis of the lung, or a fatal paroxysm occurring in the course of a chronic estivo-autumnal malaria.

EXPLANATION OF THE VARYING NUMERICAL RELATIONSHIP.

Is it possible to satisfactorily explain the varying numerical relationship of *Treponema pallidum* to those cases, on the one hand, which show characteristic tissue changes, and, on the other, to those which show no chronic lesions? Essentially, the question seems to be one of the grade of infection, although the factor of individual resistance cannot be entirely eliminated. An absolutely exact answer cannot be given, because the parental history in congenital lues is so untrustworthy. The exact period, during the intra-uterine life of the fetus, at which infection occurs cannot be accurately estimated. It seems reasonable to suppose that in the chronic cases the infection is one of only moderate severity, one which permits a reaction on the part of the tissues. In a certain percentage of such cases the development of the lesions proceeds at such a rate that the life of the fetus is finally destroyed in utero during the late months of pregnancy. In other cases, because of a still milder infection and a slower degree of development of pathological change, a living infant is born. The post-mortem findings, whether the child is still-born or is born living, are those of the classical picture of hereditary lues.

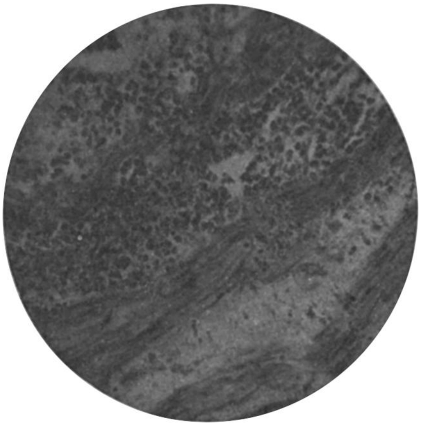

FIG. 16.—Outer portion of the wall of the umbilical vein. Separation of the muscle bundles and marked infiltration by lymphocytes. ×150.

In cases which show no chronic lesions, the ones in which organisms are so numerous, it would seem that one is dealing with an infection of extreme severity from its very inception. There results an overwhelming of the body of the fetus, causing death before there is time for the tissues to react sufficiently to lead to the development of chronic inflammatory changes. This view may appear more or less speculative. But so long as the exact moment of fetal infection cannot be determined, even speculation may help in arriving at probabilities. That there is some basis of fact in the idea expressed appears from a detailed study of the case from which Fig. 13 is derived. All of the organs of the fetus show an astonishing richness in organisms without any inflammatory changes. The outer zone of the wall of the umbilical vein (Fig. 16) shows a marked lymphoid infiltration. In these areas of pathological change treponemata are present (Fig. 17), but only in moderate numbers. An occasional large chorionic vein shows the same change in somewhat less marked degree and with fewer organisms. A study of the histopathology of this case leads to the belief that the primary localization of the parasites occurred in the walls of the umbilical and chorionic veins, and that from these foci of infection the fetus was invaded. The invasion resulted in an "Ueberschwemmung" of the fetus and in the production of death before there was time for the establishment of fetal inflammatory lesions like those present in the cord.

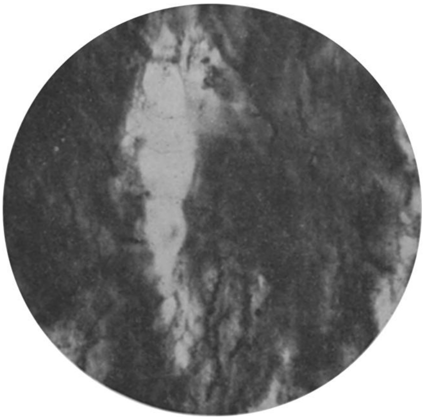

FIG. 17.—From the unbilical vein shown in Fig. 16. ×1,500.

THE CAUSES OF DEATH IN CONGENITAL LUES.

In the chronic group the lesions present offer a sufficient explanation of the cause of death. Very probably a chronic toxemia also plays some part in the death of the fetus. In the acute group death is due to the large number of organisms present, just as a streptococcus bacteriemia may cause death without the production of inflammatory lesions. Besides the cases in which fetal death is due directly to *Treponema pallidum*—either by the production of pathological changes or because of its presence in very great numbers—it is possible that syphilis on the part of the mother may cause the death of the fetus without the intervention of either of these factors. In such cases death must be due to the transmission of toxic substances from the mother to the fetus or to disturbances of fetal metabolism, and is not due directly to syphilitic involvement of the fetus. Some such mechanism as this must be the cause of fetal death in those cases in which the mother gives undoubted evidence of lues, but in which the fetus shows no chronic inflammatory changes and no treponemata.

GERMINAL INFECTION.

One is forced to consider, for a space, the possibility of germinal infection in syphilis. As our knowledge of the etiology of the infectious diseases has increased, the possibility of an infection of a germinal cell followed by the development of a specifically diseased fetus has become more and more limited. At the present time such an infection receives serious consideration only when one is dealing with tuberculosis and with syphilis. When it is borne in mind that the most probable immediate result of an invasion by the tubercle bacillus is an intra-cellular infection, which leads primarily to hypertrophy of the invaded cell and to a disturbance of its normal regulatory mechanism—a process resulting in the formation of a giant cell—the possibility of infection of an individual spermatozoon or ovum without a destruction of the viability of the cell appears extremely remote. It is true that a number of the pathogenic protozoa may invade the ovum without interfering with its further development. More particularly, the germinal infection of the secondary insect host is a phenomenon which distinguishes certain of the protozoa very sharply from the great majority of the pathogenic bacteria. While the semen in syphilis may be infectious, a parasitization of individual spermatozoa appears extremely improbable. The presence of *Treponema pallidum* within the ova of infants infected with congenital lues has been reported. I am able to confirm the correctness of this observation in one of my own cases. That an infection of an ovum of a sexually mature woman is a physical possibility must, therefore, be admitted. There is, however, ground for a difference of opinion as to the ultimate result of such an infection upon the development of the ovum after fertilization. It may be possible that the very early abortions of syphilis are the results of the infection of ova. That the development of such embryos could proceed very far does not seem probable, when one recalls that the presence of *Treponema pallidum* causes either a marked inflammatory reaction on the part of the tissues when the infection is not too severe, or death before lesions can be produced, if large numbers of organisms are concerned in the invasion. I am unwilling to admit the probability, or even the possibility, of germinal infection in those cases which constitute the condition known as congenital syphilis—infants born dead during the latter half of pregnancy and those born living at or shortly before the end of gestation and manifesting at birth or shortly thereafter the evidences of lues.

SUMMARY.

The presence of *Treponema pallidum* is the only accurate criterion for the diagnosis of congenital lues.

In infants, both still-born and born living, there occur, relatively frequently, chronic inflammatory changes which render the histological diagnosis of syphilis extremely difficult.

The essential lesion, in congenital as well as in acquired lues, is the vascular involvement. This begins with the localization of the parasites in the perivascular lymphatics, which leads first to proliferation and infiltration of the adventitia and then to a spread of the inflammatory process inward toward the lumen of the vessel as well as outward into the tissues surrounding the vessel. In the congenital form of the disease the diffuseness of the interstitial inflammation may overshadow and hide the more essential and characteristic vascular involvement.

The routine examination of all infant autopsies for *Treponema pallidum* makes possible a classification of neonatal syphilis into two groups.

In the first group belong those cases showing vascular involvement and chronic interstitial inflammatory changes.

In the second group belong cases which show none of the lesions that can be considered characteristic of lues.

In the first group organisms are, as a rule, not numerous, and death is due in part to the pathological change and in part to toxemia.

In the second group organisms are present in astonishing numbers, and death is due to an overwhelming of the fetus. Death results, possibly through acute intoxication, before there is sufficient time for a reaction on the part of the tissues.

To each group belong still-born fetuses, as well as infants born living.

That the cases of congenital syphilis born during the latter half of pregnancy are the results of germinal infections appears improbable and impossible.